REMARKS

Claims 1-17 and 22-23 are currently pending in the present application. Claim 1 has been amended and new claim 23 has been added in the expectation that the amendments will place this application in condition for allowance. The amendments do not introduce new matter within the meaning of 35 U.S.C. § 132. Accordingly, entry of the amendments is respectfully requested.

1. Objection to claim 1

Claim 1 has been objected to for the following informalities: improper punctuation. In particular, the Official Action states the following: "There is a period at the end of step (f) in claim 1, where it is believed there should be a semicolon. Appropriate correction is required."

Applicants thank the Examiner for her comments and suggestions regarding the claim. Accordingly, applicants have amended claim 1 to correct the punctuation by removing the period and inserting a semicolon in its place.

Accordingly, applicants respectfully request the Examiner withdraw the objection to claim 1.

2. Rejection of claims 1-5, 9-17 and 22 under 35 USC §102(b)

Claims 1-5, 9-17 and 22 stand rejected under 35 USC §102(b) as being anticipated by Dahiyat et al. (Protein Science, 1996, Vol. 5,

895-903).

Applicants respectfully traverse this rejection. The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

The presently claimed subject matter in claims 1-5, 9-17 and 22 relates to a computer-implemented method for predicting at least one amino acid sequence compatible with a specified three-dimensional (3D) structure of a protein or peptide by providing a coordinate set representing the backbone of said 3D structure; constructing a reduced virtual representation for the 3D structure; determining for each position along the virtual structure representation its solvent accessibility; constructing an initial amino acid sequence by randomly assigning for each position along the structure an amino acid residue selected randomly from a predefined group of amino acids having a solvent accessibility compatible with the solvent accessibility of said position; randomly selecting one or more positions along the sequence and

applying on each position a Monte-Carlo simulation in sequence space and rotamer space; expanding the reduced representation of the virtually represented amino acid sequence to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the predefined 3D structure; and optionally creating a computer output of the expanded all-atom representation of the primary structure.

Dahiyat et al., however, does not teach each and every limitation of the claims as required by *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. In fact, the computer-implemented prediction method of the presently claimed invention differs substantially from the teachings of the Dahiyat reference in at least three substantial ways.

The presently claimed invention (enumerated in step (b) of claim 1) makes use of a reduced representation of the virtual predefined 3D structure. According to one embodiment of the invention, based on the simplified representation of Herzyk and Hubbard (see page 9 of the specification), amino acids within the randomly selected sequence are represented by virtual spherical atoms, wherein the main chain of the protein, polypeptide or any other suitable polymer is represented by one virtual atom per residue located at the Cα position and the side chains are represented by one or more additional virtual atoms. The use of a

reduced representation for the 3D structure increases the efficiency of the method as it reduces the set of allowed rotamers for each side chain.

In contrast, Dahiyat et al. do not teach constructing a reduced virtual representation for the predefined 3D structure, and therefore does not teach each and every limitation of the presently claimed invention.

Additionally, in step (c) of claim 1, in order to reduce the number of possible sequences searched, the number of possible amino acids at different positions in the sequence is reduced by defining for each position its solvent accessibility and selects for each position only the amino acids which are compatible with the solvent accessibility assigned to the position. This greatly enhances the efficiency of the method of the presently claimed invention by narrowing the required search to only those solvents compatible with the solvent assigned to a particular position.

In contrast, Dahiyat et al. do not teach determining for each position along the virtual structure representation its solvent accessibility, and therefore does not teach each and every limitation of the presently claimed invention.

Furthermore, the presently claimed invention makes use of a unique scoring function which applies part of a Monte-Carlo simulation while combining a search in the sequence space for amino acid residues and the specific rotamer space of each residue. The

unique scoring function of the presently claimed invention uses the Monte Carlo (MC) search in sequence space, combined with all possible conformations of up to three (3) residues, which are allowed to be mutated at the same time.

In contrast, Dahiyat et al. teach a Dead-End Elimination (DEE) algorithm which includes exhaustive enumerations of states, as the optimization algorithm. As conceded by the Examiner, the use of a MC search in the protein design automation (PDA) is only after completing the DEE. "A Monte Carlo search was then executed, starting at the optimal sequence in order to find other high-scoring sequences." (See Abstract) The MC is performed by Dahiyat only in order to overcome the possible differences between the theoretical and the actual potential surfaces and according to Dahiyat's 'fine tuning' with MC, residues are changes at random positions, to find the best actual potential surface. It should be noted that the 'fine tuning' according to the presently claimed invention is not achieved by MC, but rather by molecular dynamics (as detailed on page 14).

Accordingly, the Examiner has failed to show a prima facie case of anticipation as the Dahiyat et al. reference does not teach each and every limitation of the claims as required by *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131.

Accordingly, applicants respectfully request the Examiner to

reconsider and withdraw the rejection of claims 1-5, 9-17, and 22.

3. Rejection of claims 6-8 under 35 U.S.C. §103(a)

The Official Action states that claims 6-8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Dahiyat in view of Hurley et al.

Applicants respectfully traverse the rejection of claims 6-8. The references of record does not teach or suggest applicants' inventive subject matter as a whole as recited in the claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

The presently claimed subject matter in claims 6-8 relates to a computer-implemented method for predicting at least one amino acid sequence compatible with a specified three-dimensional (3D) structure of a protein or peptide by providing a coordinate set representing the backbone of said 3D structure; constructing a reduced virtual representation for the 3D structure; determining for each position along the virtual structure representation its solvent accessibility; constructing an initial amino acid sequence by randomly assigning for each position along the structure an amino acid residue selected randomly from a predefined group of amino acids having a solvent accessibility compatible with the solvent accessibility of said position; randomly selecting one or more positions along the sequence and applying on each position a Monte-Carlo simulation in sequence space and rotamer space; expanding the reduced representation of the virtually represented amino acid sequence to its corresponding all-atom sequence representation thereby obtaining an amino acid sequence compatible with the predefined 3D structure; and optionally creating a computer output of the expanded all-atom representation of the primary structure, wherein for each position along the 3D structure its solvent accessibility is determined according to the extent of exposure of said position to the solvent surrounding it, wherein said solvent is substantially water.

In contrast, as outlined above, Dahiyat et al. do not teach

the computer-implemented prediction method of the presently claimed invention. The presently claimed subject matter differs substantially from the teachings of the Dahiyat reference in at least three substantial ways. In particular, Dahiyat et al. do not teach (1) constructing a reduced virtual representation for the predefined 3D structure, (2) determining for each position along the virtual structure representation its solvent accessibility, or (3) a unique scoring function which applies part of a Monte Carlo simulation while combining a search in the sequence space for amino acid residues and in the specific rotamer space of each residue. These distinctions are not minimal and are limitations that are recited in the presently pending claims, which define the present invention over the Dahiyat et al. reference.

The Hurley et al. reference does not remedy these deficiencies. Hurley et al. teach that water could be a common solvent. Hurley et al. make use of a given specific sequence and performs alternative replacements of only buried residues, in order to determine the effect of these changes on stabilization of the protein. As such, the Hurley et al. analysis is focused upon only a small portion of the entire protein, which includes only the hydrophobic core packing arrangements.

Additionally, Hurley et al. make use of a very different scoring methodology than does the presently claimed invention. In particular, different local mutations are scored by applying Free-

Energy Calculations using a modified Molecular Mechanics force field (AMBER). As will be appreciated by those skilled in the art, this method is extremely time consuming and can be applied only to very small and localized mutations. This means that when global optimization is required, as in the present method, the AMBER approach cannot be employed. In this regard, it should be noted that the use of Molecular Mechanics force field in the present invention is only as a tool for refinement of the final solution. In other words, after determining the best sequences, the reduced representation and the Molecular Mechanics force field is applied in order to validate that the transformation to the full atom representation did not impair optimization.

Even if one would consider combining the Dahiyat publication with the Hurley et al. reference, he would, at best, improve the results obtained by the method of Dahiyat, however, would not reach the optimization level achieved in the present invention.

Accordingly, applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 6-8.

CONCLUSION

Based upon the above remarks, the presently claimed subject matter is believed to be novel and patentably distinguishable over the prior art of record. The Examiner is respectfully requested to enter the above claim amendments and allow this case to proceed to

grant. Favorable action with an early allowance of the claims pending in this application is earnestly solicited.

The Examiner is welcomed to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

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